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DCTD Concept for the RFA

Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24)
&
Cancer Immunological Data Commons (CIDC) for the CIMACs (U24)

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NCI-supported Immunotherapy Trials

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Between 2010 -2015

- **88 Phase I-III immunotherapy trials were activated in the DCTD Clinical Trial Network** (NCTN, ETCTN, CITN, and PBTC)
- **8 Phase III trials, 14 Randomized Phase 2 trials**
- **Clinical settings:** common, rare tumors; neoadjuvant, adjuvant and metastatic disease
- **Study regimens include single agent and novel combinations**

Check point inhibitors
- Anti- CTLA-4 (Ipilimumab, tremelimumab)
- Anti-PD-1 (Nivolumab, Pembrolizumab)
- Anti-PD-L1 (MEDI4736 and MPDL3280A)

Cytokine:
- IL-15
- IL-12

Vaccine
- CDX1401 (against NYSO-1)
- PSA PROSTVAC/TRICOM
- CEA TRICOM/PANVAC
- **Other:** peptide (gp100, HPV, RAS, P53, MART and others)

Oncolytic virus:
- T-VEC

T-cell engaging bispecific Ab
- CD19 BiTE (Blinatumomab)

Other immune modulators:
- IDO (INDB0243360) ~ 2 trials
- Lenalidomide, Pomalidomide: -
- FLT3 ligands
- Anti-CD27 mAb (CellDex)

Most randomized trials have mandatory collection of baseline tissues/blood
Many early clinical trials include serial biopsies
Definition of immunotherapy trials excludes MAbs directed at tumor targets or vasculature (e.g., cetuximab or bevacizumab)

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Biomarkers are Critical to Further Development of Cancer Immunotherapy

- **Immunotherapy has remarkable activity in a variety of cancers, but only a minority of patients benefit:**
  - RR in most of the "responsive" tumors is 20-30%; Some tumors do not respond (pancreatic cancer, MMR+ colon cancer, myeloma).

- **Strategies to optimize patients' outcome will rely on:**
  - **Combination therapies** to overcome intrinsic or acquired resistance.
  - **Biomarkers** – especially predictive markers to provide the right treatment to a given patient.

- **Several categories of biomarkers can benefit immunotherapy:**
  - Predictive of benefit from drug intervention and toxicity
  - Target modulation and rational design of combination therapy.
  - Response to therapy and monitoring.
  - Dose selection using pharmacogenomic markers.

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Current DCTD Trial Networks Have Limited Capabilities for Effective Biomarker Studies

- "Fit-for-purpose" validated biomarker assays are **not available** to individual sites involved in the trial including early and late stage trials.
- Different laboratories may use **different platforms** for the same markers:
  - Duplicative efforts in assay development/validation.
  - Differences in scoring and reporting standards, high variability limiting integrative analyses.
- **Lack of databases** and informatics tools suitable for the complexity of immune biomarkers/platforms, and for integration of data from multiple trials.

Common assays and biomarkers of interest

- **Tumor genomics and neoantigen analysis**
  DNA-seq and RNA-seq ; prediction of class I and II neoantigens
- **T-cell clonality** (TCR sequencing)
- **Functional profiling/signature:** Cytokine panel; Nanostring
- **In situ assays IHC, multiplex QIF (**T cells and B cell subsets, macrophages, dendritic cells, MDSC, NK cells)
- **Tumor/blood:** soluble single cell profiling using the 38-marker CyTOF panel

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Overall Needs/Solutions to Improve Assay Development for Immunotherapy

DCTD Cancer Immunotherapy Workshop, January 14-15, 2016

Needs	Solutions
1. Sample collection	Specimens from clinical trials
2 Sample analysis requires multiparametric algorithms	Multidisciplinary team and computational resources
3. Data harmonization, integration and modeling; open access database	Bioinformatics and centralized database “Immunomine”
4. Standardized quality controlled assays	Centralized laboratory

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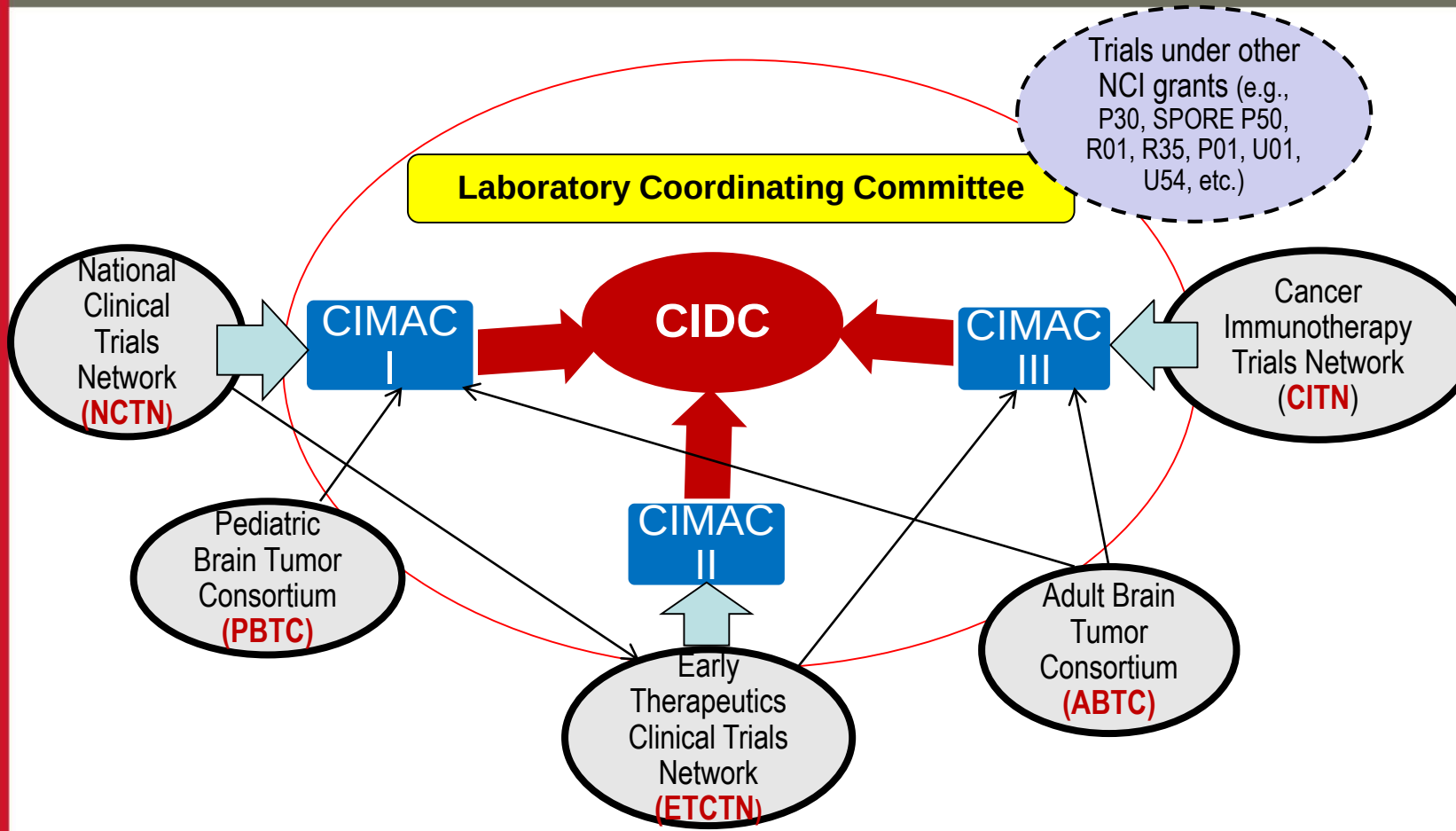
Laboratory Network of Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24) and Cancer Immunologic Data Commons (CIDC) (U24)



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CIMACs - General Role

- **Cancer Immune Monitoring and Analysis Centers (CIMACs) - up to 3 awards:**
  - **Conduct correlative studies** and provide **immunoprofiling analyses** for specimens from NCI-supported clinical trials:
    - **NCI-supported Phase 0-2 clinical trial(s)** conducted within DCTD-supported networks/consortia (NCTN, ETCTN, CITN, PBTC, and ABTC).
    - Perform correlative studies **in NCI-supported clinical trials from outside** the established network/consortia (grant mechanism).

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CIMAC – Specific Functions

- Each “Center” in the network should be self-sufficient to conduct biomarker studies for a group of clinical trial sites and collaborate closely with **clinical investigators and study statisticians.**
- Provide service and **multidisciplinary expertise** (immunology, pathology, molecular biology) for:
  - **Use of well-defined**, fit-for-purpose assays for retrospective and prospective analysis.
  - **Scale-up assays** that need to be refined or that need to undergo analytic validation and clinical validation.
  - Some of the assay capacities may be **shared across the CIMACs.**
- Provide **computational biology and biostatistics** resources for high-throughput data analysis; specific projects require specific statistical tools and approaches.

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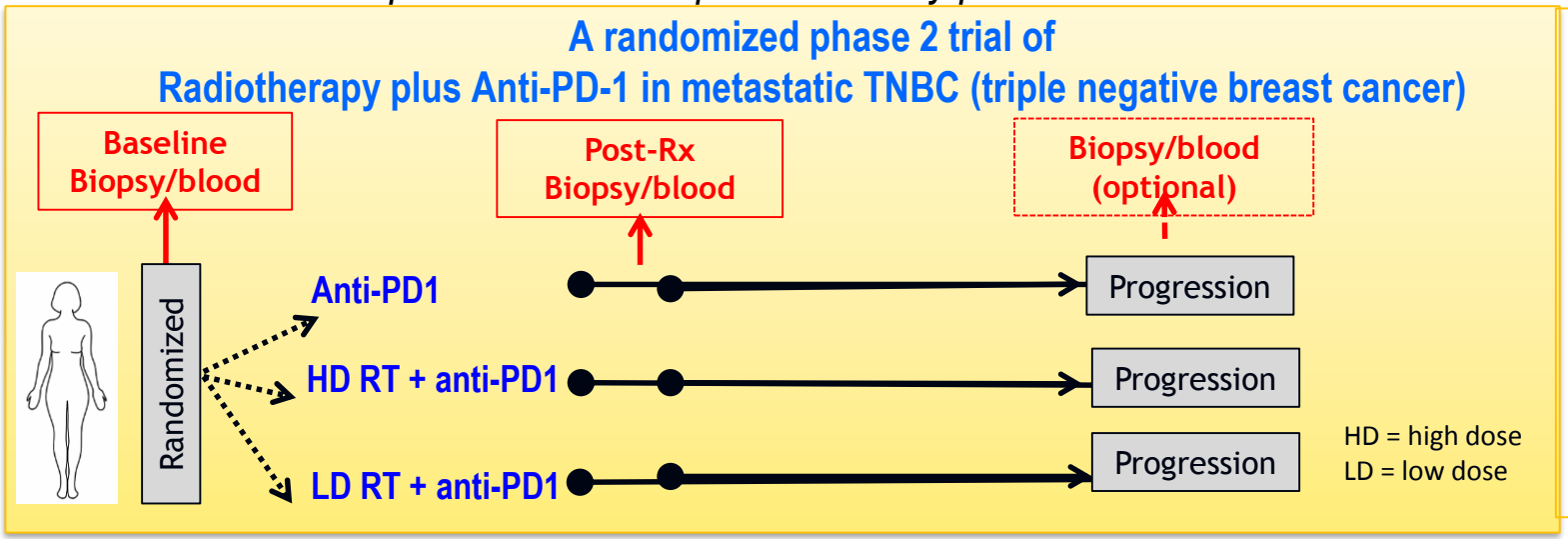
Biomarkers – The Validation Process

- A. Define what the biomarker is supposed to predict (fit-for-purpose).
- B. Determine how strong the predictive power needs to be useful for clinical decision-making.
- C. Confirmation of candidate biomarker(s) or omics-based test in preliminary study.
- D. Development of a candidate biomarker standardized assay (a single marker or multi-variate algorithm).
- E. Testing of a biomarker(s) in a training set; cut point to link measured values to clinical endpoint.
- F. Lockdown of the assay and the discriminating algorithm.
- G. Determine the locked down assay association with a specific clinical endpoint in an independent data set (validation set).

An example of biomarker questions early phase II clinical trials



Examples of candidate biomarker panels:
- TILs, PD-L1
- WES/RNA-seq,
- TCR clonality,
- Cytokine panel,
- GEP
- Flow/CyTOF

- **Hypothesis**: RT may enhance anti-PD-1 activity by inducing pro-inflammatory tumor microenvironment.
- **Primary objective of the trial:** Response rate improvement by combination RT/anti-PD1 vs. anti PD1 monotherapy (e.g., 55% vs. 25%; 40 pts/arm).
- **Biomarker objectives (ancillary endpoints):**
  - Target modulation (pre- and post-Rx biopsies/blood):
    - Induced proinflammatory TME e.g., TIL, neoantigens, T-cell clonality, and i PD-L1 in response to RT.
  - Predictive markers:
    - Correlation of biomarker(s) at baseline with mono and combination therapy.

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How biomarkers in this trial might be used in this trial and inform further development?

- Comparisons between two treatment arms; assume N = 40 per arm
- Example of analysis based on TIL by H&E at 50% cutoff
- Power to detect difference in response rate between immunotherapy alone (IMMUNO) versus immunotherapy + radiotherapy (IMMUNO+RT)
  - e.g., 25% vs 55%, power 80%
- Assumed interaction between TILs and treatment arm (RR in **TIL-pos** 45% in IMMUNO vs. 50% in IMMUNO+RT; in **TIL-neg** 10% RR in IMMUNO vs. 40% in MMUNO+RT).
- Power to detect interaction effect in a two arm trial with total sample size N=80 (40/arm)
  - Prevalence of TIL-pos 40%, power 67% (1-sided level test)
- Future study: Validation of clinical utility in phase III trials Anti-PD1 +/- RT (retrospective or prospective)

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CIMAC - Examples of Immuno-Oncology Assays and Cost Estimate

Specimen collections are covered by Clinical Trial Networks/Consortia or grants

Platform	Assay	Cost
Preanalytics	Blood/plasma/tissue processing	$760
Immunohistochemistry (IHC), Microscopy	Protein expression	$250/slide
Flow Cytometry	Immunophenotyping, Cell sorting	$140/hr
Mass Cytometry (CyTOF	Immunophenotyping	$140/hr
Enzyme-Linked ImmunoSpot (ELISpot)	Functional analysis of T/B cells	$510/plate/each
Enzyme-linked Immunosorbent Assay (ELISA)	Functional analysis of immune response	$300/ plate
Affymetrix U133 plus 2.0 Array	Gene expression analysis of tumor biopsies	$590/sample
Whole Exome Sequencing (WES) per tumor/normal pair	Mutational load-assay Computer server	$3,219 $200
In silico Bioinformatics	T cell epitope prediction	$140/hour
TCR sequencing	T cell receptor clonality	$1,000/sample
RNAseq	Gene expression Computer server	$1,268 $200
Biostatistics and Computational resource	Data analysis and interpretation Statistical support	$120/hr

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CIDC - Data Quality and Harmonization

- **Cancer Immunologic Data Commons (CIDC) - single site.**
- **Bioinformatics Core** will be responsible for**:**
  - Serves as a repository for collection of data on the studies completed by the CIMACs.
  - Collaboration with the CIMACs to facilitate standardization of **immunologic data collection** and fostering best practices among the CIMACs and their clinical collaborators.
  - Development of information resources and **sharing the data** with other investigators to promote secondary data analyses.
  - Collaboration with **data centers** (e.g., Genomics Data Commons), whenever possible.

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CIDC - Functions and Cost Estimate

Resources	Function	Cost
Bioinformatics and biostatistics resources to provide high performance computing (HPC) resources in collaborations with laboratory centers and NIH resources	Scientific consultation Data collection and management High throughput computational analysis and Integration Data standards normalization Database development	$120/hr Two biostatiscs and bioinformatics experts
Analytical tools	Software development Web tools	$120/hr
Storage space	Data storage	$1.2 pr GB per year
Data interpretation platforms	Ingenuity Gene Spring	$1,200/subscription/year $2,300/subscription/year
Computer/Data servers		$140/hr

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CIDC - Administrative Core and LCC

- **CIDC Administrative Core** will be responsible for:
  - Logistical assistance in arranging network meetings, webinars and workshops.
  - Management of resources that are reserved for supporting studies from outside the pre-arranged alliances with clinical trials networks/consortia.

- **A Laboratory Coordinating Committee (LCC) -** a governing body of the network will be responsible for:
  - Strategic planning and prioritization of scientific questions regarding optimization of resources for correlative studies.
  - Overseeing and coordinating the integration efforts among CIMACs.
  - LCC will include representatives of the CIMACs, CIDC and the NCI.

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Network's Annual Budget

CIMACs R24

• Laboratory Centers*	$3,200K
• Scientific Leadership	$950K
• Network meetings/travel	$50K
• **Direct Costs**	**$4,200K**
• **Total Costs**	**$6,500K**

*Expected: 360 patients/year
(at $8,000/patient)

CIDC R24

• Scientific Leadership	$350K
• Bioinformatics Analysis	$150K
• Computers/Data Servers	$120K
• Database Systems Access	$20K
• Network meeting/travel	$10K
• **Direct Costs**	**$650K**
• **Total Costs**	**$1,000K**

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Review Criteria for CIMACs Applications

- Expertise in providing molecular and cellular biomarker assays services.
- Personnel qualifications.
- Past experience.
- Competence in specific platforms/assays capabilities.
- Experience in collaborations with clinical centers.
- Expertise in biostatistics and bioinformatics, including infrastructure in analysis of high-throughput omics data.